REMARKS/ARGUMENTS

Claims 2, 10, and 18 have been revised to incorporate the features of claims 3, 11, and 19, respectively, without prejudice for re-presentation of the subject matter of original claims 2, 10 and 18 in a continuing application. The revisions to the claims better tailor the claims to currently contemplated commercial embodiments of the invention. Thus the changes are made for business reasons and not in acquiescence to any rejection of record.

No new matter has been introduced, and entry of the revised claims is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

Claims 2, 4-10, 12-18, and 20 were rejected under 35 U.S.C. §112, first paragraph, as allegedly based on a non-enabling disclosure. The statement of the rejection is based upon an interpretation of paragraph [0005] on page 1 of the instant application as well as an allegation of "criticality" of "small" RNase inhibitors.

Applicants respectfully point out that the position set forth by this rejection has been obviated in light of the above revisions to the claims. Accordingly, this rejection may be properly withdrawn.

Additionally, Applicants point out that nowhere within paragraph [0005] is the concept of "criticality" discussed, either explicitly or implicitly. Moreover, paragraph [0006] on page 1 specifically points out that the statements in paragraphs [0003] to [0005] "do not constitute any admission".

Rejections under 35 U.S.C. §102

Claims 2 and 18 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Star et al. (USP 6,790,636). Applicants have carefully reviewed the statement of the rejection and the cited Star et al. document.

Applicants respectfully submit that Star et al. provide no teaching, suggestion, or other indication regarding the use of a ribonucleoside vanadyl complex (RVC). Accordingly, Applicants respectfully submit that this rejection may be properly withdrawn.

Rejections under 35 U.S.C. §103

Claims 1-20 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable in light of Star et al. (USP 6,790,636) and Schwartz et al. (USP 6,306,612) in view of Berger et al. (Biochemistry 1979, 18:5143) and Kanz et al. (Exp. Hematol. 1988, 16:394). Applicants have carefully reviewed the statement of the rejection and the cited documents and respectfully submit that no *prima facie* case of obviousness has been presented.

As an initial matter, Applicants understand the rejection to be based on a combination of all four cited documents such that none of the documents are relied upon in the alternative. If this is incorrect, clarification of the basis of the rejection is respectfully requested.

Turning to the basis of the rejection, Applicants again point out that, as noted above, Star et al. provide no teaching, suggestion, or other indication regarding the use of a ribonucleoside vanadyl complex (RVC).

Similarly, Schwartz et al. provide no such teaching, suggestion or indication regarding RVC. To the contrary, the specific portion of the Schwartz reference quoted in the statement of the rejection as teaching "precaution against Rnases were taken" was only in the context of fixing a cell containing sample via 4% paraformaldehyde, dehydration, and paraffin embedding (see column 11, lines 54-59). This fixed tissue was then sectioned at 5 micron intervals before any immunohistochemistry (IHC) related action was taken. Thus there was no teaching, suggestion or other indication of any "precaution against Rnases" during IHC. In light of this very limited discussion by Schwartz et al., Applicants respectfully submit that this document fails to support the instant rejection.

Kanz et al. only disclose the use of "vanadyl-ribonucleoside complexes" during the preparation/acetylation of slides, which is prior to the attachment of cells (see page 394, right column, last full paragraph), and as part of the pre-hybridization preparation for *in situ* hybridization (see page 396, last full paragraph, and page 397, Figure 2; and page 399, left

column, lines 12-16). Thus there were no complexes present when the cells were treated with antibodies as part of the fluorescence activated cell sorting (FACS) used to collect cells for attachment to the slides. The treatment with antibodies for FACS was also prior to the pre-hybridization steps leading up to the *in situ* hybridization. Therefore, there is no teaching, suggestion, or indication that the complexes could be successfully used in combination with an antibody reagent, such as in FACS or IHC.

Berger et al. only disclose the use of RVC during isolation of messenger ribonucleic acid from resting lymphocytes. There is no teaching, suggestion, or indication that RVC could be successfully used during IHC, such as in combination with an antibody reagent. Moreover, Berger et al. describe the RVC as "useful for producing intact RNA [but] cannot be used to inhibit nucleases during the assay for protein synthesis" (see page 5148, right column, first full paragraph). The description goes on to note that "translation in wheat germ system was virtually eliminated" due to RVC. Thus Berger et al. provides the observation that RVC can be inhibitory against other proteinaceous complexes, such as those involved in protein synthesis. Therefore, and based on Berger et al., the artisan of ordinary skill would not know definitively whether RVC would be inhibitory during an IHC process. Absent such knowledge, no expectation of success in including RVC during IHC could have been present without the guidance of the instant application.

In light of the above, Applicants respectfully point out that no *prima facie* case of obviousness has been presented because 1) no adequate motivation to combine the cited documents is present; 2) no adequate expectation of success is present; and 3) the rejection appears to be based on impermissible hindsight reconstruction.

With respect to point 1, Applicants respectfully submit that given the Star et al. disclosure regarding laser capture microdissection, why would the artisan of ordinary skill look to the FACS based methods of Kanz et al. or the mRNA isolation methods of Berger et al.? The disclosure of Schwartz et al. provide no motivation for the combination given that they only discuss a "precaution" during preparation of the paraffin embedded sample.

In the absence of an adequate motivation to combine, the instant rejection appears to be based upon the presence of various features of the claimed invention in disparate

documents that are then brought together to allege obviousness. The rejection thus appears to be based upon an improper motivation "to try" to use the combination of IHC and an RVC. Applicants respectfully submit that this is contrary to the standards for a *prima facie* case as set forth at MPEP 2143.01 and the cases cited therein. The instant rejection may be properly withdrawn for this deficiency alone.

Turning to point 2, Applicants respectfully point out that there is simply no expectation in any cited document that RVC could be successfully used in combination with the reagents necessary for IHC. For example, and assuming only for the sake of the rejection's allegation that there is motivation to inhibit RNases, why was there no inhibitor like RVC used in the FACS methodology of Kanz et al., which included the use of antibodies? After all, the ultimate goal for Kanz et al. to detect mRNAs *in situ* was supplemented by inclusion of the inhibitor in the pre-hybridization steps as part of the *in situ* hybridization. Thus Kanz et al. included the complex in the preparation of the slides for attachment and in the pre-hybridization steps after FACS but not during FACS mediated cell collection. Given the concern about RNAse activity, why would the inhibitor be used to prepare the slides but not during the FACS protocol to collect cells for the slides? Why was no inhibitor used until the pre-hybridization step? After all, the Kanz et al. objective of *in situ* hybridization could only benefit from the preservation of RNA from degradation by use of an RNAse inhibitor.

The absence of an inhibitor during the antibody mediated FACS process is a particularly important indication of non-obviousness because Kanz et al. were trying different steps and combinations to stabilize mRNA to improve their *in situ* hybridization process (see pages 397-399, Discussion section).

Given Kanz et al.'s failure to provide an expectation of success in using an RVC with an antibody reagent against a cellular antigen or epitope, it is not surprising that Star et al. and Schwartz et al. also fail to teach or suggest the use of an RVC in combination with any antibody type reagent. Berger et al. simply dealt with a different methodology that did not involve antibodies and so cannot provide any expectation of success. To the contrary, Berger et al. describe RVC dependent inhibition of protein synthesis, which indicates that RVC would not be expected to be compatible with some proteinaceous complexes in a cell. Because the

antibody containing complex formed during IHC is a proteinaceous complex, Berger et al. would suggest that it is not predictable as to whether RVC would inhibit such a complex.

Given the above deficiencies of the cited documents, Applicants respectfully submit that no *prima facie* case of obviousness is present as required by the standards set forth at MPEP 2143.02 and the cases cited therein. Absent the required expectation of success, the instant rejection may be properly withdrawn.

As for point 3, Applicants respectfully point out that absent both an adequate motivation to combine and an expectation of success, the instant rejection appears to be based upon an improper hindsight reconstruction of the claimed invention using Applicants' own disclosure as a guide. This is expressly held to be improper for establishing a *prima facie* case of obviousness (see MPEP 2142 and the cases cited therein). Accordingly, the instant rejection may be properly withdrawn for this reason alone.

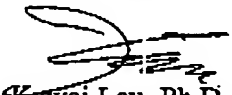
In light of the foregoing, Applicants respectfully submit that no adequate case of obviousness has been presented and this rejection may be properly withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100.

Respectfully submitted,



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